

# Robustness Leads Close to the Edge of Chaos in Gene Regulatory Networks

Nen Saito

Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan  
Cybermedia Center, Osaka University, Toyonaka, Osaka 560-0043, Japan and  
Graduate School of Arts and Sciences The University of Tokyo 3-8-1 Komaba,  
Meguro-ku Tokyo 153-8902, Japan (present address)\*

Macoto Kikuchi

Cybermedia Center, Osaka University, Toyonaka, Osaka 560-0043, Japan and  
Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan †  
(Dated: March 4, 2013)

Transcriptional dynamics of gene regulatory networks are regulated in highly precise manner, despite a fluctuating environment and mutations. We model these dynamics as those of a coupled logistic map on a network and design systems which are robust against phenotypic perturbations (perturbations in dynamics), as well as systems which are robust against mutation (perturbations in network structure). To achieve such a design, we apply a multicanonical Monte Carlo. Analysis based on the maximum Lyapunov exponent and parameter sensitivity shows that systems with marginal stability, which are regarded as systems at *the edge of chaos*, emerge when robustness against genotypic perturbations is required. This emergence of *the edge of chaos* is a self-organization phenomenon and does not need a fine tuning of parameters.

PACS numbers: 87.16.Yc, 87.18.Cf, 87.23.Kg

Keywords: gene regulatory network, edge of chaos, robustness, self organization, multicanonical Monte Carlo

Gene expression in living cells is a highly complex process, achieved through a network of mutual regulation between numerous genes. Transcription-translation regulation is robust against both phenotypic and genotypic perturbations [1–3]. Put differently, gene expression patterns are kept stable in spite of intrinsic and extrinsic noise (i.e., phenotypic perturbations) and mutations (i.e., genotypic perturbations). It seems reasonable to think that robustness against phenotypic perturbations has been evolutionarily developed for adapting to noisy environments. There are also several advantages in having mutational robustness - it buffers against deleterious mutations, and it has been recently suggested that mutational robustness enhances evolvability [1, 3, 4].

Robustness, as described above, is a fundamental property of life. This point of view naturally gives rise to the question: what kind of system emerges when only robustness is required? In this paper, we show that systems at the *edge of chaos* are selected with only the requirement of mutational robustness.

It has long been hypothesized that living systems favor the *edge of chaos*, where stability and chaoticity co-exist. Originally, Kauffman [5] introduced the Boolean network model (N-K model) as a model of a gene regulatory network, and proposed the hypothesis that living systems prefer *the edge of chaos* because it allows systems to have complex behaviors [5]. Here we propose an alternative scenario, specifically that the requirement of having mutational robustness drives living systems to *the*

*edge of chaos*, regardless of whether or not living systems prefer it.

We propose a coupled map system as an abstract model of a gene regulatory network. Unlike the N-K model, each element in this model has its own dynamics. Assuming that  $x_i^t \in (-1, 1)$  is the gene expression of the  $i$ -th gene at time step  $t$ , the single gene dynamics are written as  $x_i^{t+1} = G(x_i^t)$ . These dynamics mimic multiple processes in an expression of a single gene. In the presence of  $N$  genes, the dynamics of  $x_i^t$  are expressed as

$$x_i^{t+1} = (1 - \epsilon)G(x_i^t) + \epsilon \sum_j^N W_{ij}G(x_j^t), \quad (1)$$

where  $\epsilon$  is a coupling constant.  $W_{ij}$  describes the interaction strength from gene  $j$  to gene  $i$ ;  $W_{ij} \in [0, 1]$  satisfies both conditions  $W_{ii} = 0$  and  $\sum_j^N W_{ij} = 1$  for each  $i$ . We call the matrix  $W$ , whose  $ij$  element is  $W_{ij}$ , a network. Here we choose the logistic map  $g(x, a) = 1 - ax^2$  as  $G(\cdot)$ . We use the model parameters  $a$  and  $\epsilon$  as  $(a, \epsilon) = (1.8, 0.1)$ . This choice indicates that a single disconnected gene exhibits chaotic dynamics. We impose an additional constraint on  $W$ : the number of input links  $k$  to each gene is fixed. We note that in the case of  $W_{ij} = 1/(N - 1)$  for all  $(i, j)$ , the system becomes the globally coupled map (GCM) [6] and it shows highly chaotic behaviors at the parameters  $(a, \epsilon) = (1.8, 0.1)$ . In contrast to the N-K model, variables of this model take continuous values and a linear stability analysis can be applied.

In this model, a network  $W$  is regarded as a genotype while an attractor of dynamics  $\mathbf{x}^t$  is regarded as a phenotype. Our goal is to design networks under the

\* saito@complex.c.u-tokyo.ac.jp

† kikuchi@cmc.osaka-u.ac.jp

two different design principles: robustness against phenotypic perturbations (i.e., perturbations in the dynamics of gene  $\mathbf{x}$ ) and robustness against genotypic perturbations (i.e., perturbations on network  $W$ ). In both cases, only network  $W$  is tuned.

Let us start with the first design principle, namely robustness against perturbations in dynamics. In other words, we are aiming to design a system with a stable attractor. For this end, we use Lyapunov exponent analysis and a multicanonical Monte Carlo [7, 8].

Once a network  $W$  is given, the finite time maximum Lyapunov exponent  $\lambda_1$  [9] is calculated for the dynamical system in Eq. (1), starting from a given initial state  $x_i^{0*}$  [10]. We perform the simulation up to  $T = 1500$  and regard the first  $T' = 1000$  steps as transient and discard them.

Multicanonical Monte Carlo [7, 11] allows us to sample networks with negative  $\lambda_1$ , which indicates that a network is stable, and to estimate the probability of a stable network. Our multicanonical Monte Carlo strategy adopted in this study is to perform random walks in  $\lambda_1$  space and thereby to sample rare networks that have negative  $\lambda_1$ . We define the density of  $\lambda_1$  as

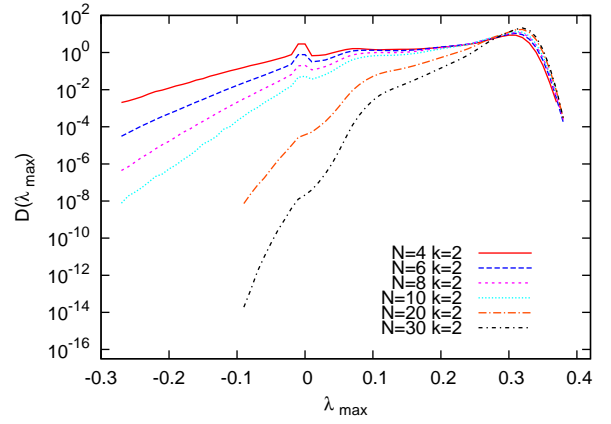
$$D(\lambda) = \int_0^1 \delta(\lambda_1(W) - \lambda) p(W) \Pi_{i,j} dW_{ij},$$

where  $\delta$  is the Dirac  $\delta$ -function, and  $p(W)$  is the probability density that a network  $W$  appears under random sampling. We consider here a network ensemble in which  $p(W)$  is given by

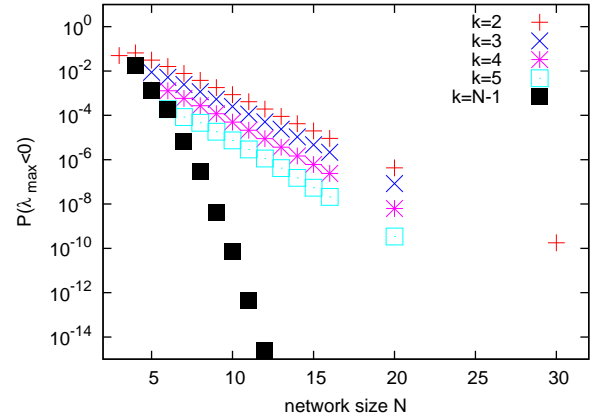
$$p(W) \propto \Pi_i \delta(\sum_j W_{ij} - 1) \delta(\sum_j \theta(W_{ij}) - k) \delta(W_{ii}), \quad (2)$$

where  $\theta(z)$  is a function that satisfies  $\theta(z) = 1$  for  $z \neq 0$  and  $\theta(z) = 0$  for  $z = 0$ . A key quantity of multicanonical Monte Carlo is the weight function  $w(\lambda_1)$  of  $\lambda_1$ . In this study, the Wang and Landau algorithm [12] is used to tune the weight function  $w(\lambda_1)$ . Performing Monte Carlo sampling with the weight  $w(\lambda_1)$ , we modify  $w(\lambda_1)$  step by step until the histogram  $h(\lambda_1)$  of  $\lambda_1$  is sufficiently flat. In practice, we calculate the density  $D(\lambda_1)$  only in the prescribed interval  $\lambda_a < \lambda_1 < \lambda_b$ . Details of the implementation are given in the supplementary material (ST1).

Figure 1 shows the calculated densities  $D(\lambda_1)$  of  $\lambda_1$  for the fixed input degree  $k = 2$ . We also show  $D(\lambda_1)$  for  $k = 3 \sim 5$  in the supplementary material (SF1 - SF3). Using density  $D(\lambda_1)$  in Fig. 1, the probability that networks with negative  $\lambda_1$  are observed under random sampling is calculated by  $P(\lambda_1 < 0) = \int_{\lambda_a}^0 D(\lambda_1) d\lambda_1$ . We estimate  $P(\lambda_1 < 0)$  with  $k = 2 \sim 5$  and  $k = N - 1$ , which are shown in Fig. 2. Each  $P(\lambda_1 < 0)$  shows that a stable attractor becomes increasingly rare as  $N$  or  $k$  increases, indicating that these systems are in the chaotic phase (we define that a system is in the chaotic phase when only positive values of  $\lambda_1$  appear as  $N \rightarrow \infty$ ). These results are consistent with the behavior of GCM with  $(a, \epsilon) = (1.8, 0.1)$  [6].



**FIG. 1:** (COLOR ONLINE) Density of finite time Lyapunov exponent under random sampling of networks with input degree  $k = 2$ . Calculated in the prescribed interval  $-0.28 < \lambda_1 < 0.39$  for  $N = 4 \sim 10$  and  $-0.1 < \lambda_1 < 0.39$  for  $N = 20$  and 30.

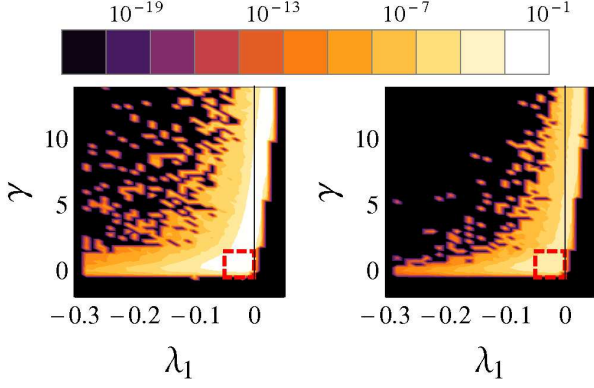


**FIG. 2:** (COLOR ONLINE) Network size dependence of the probability  $P(\lambda_1 < 0)$  of networks with negative  $\lambda_1$ . The logarithms of  $P(\lambda_1 < 0)$  for  $k = 2 \sim 5$  decrease linearly or slightly faster than linear as functions of  $N$ . The logarithm of  $P(\lambda_1)$  for  $k = N - 1$  decreases quadratically.

Using the second design principle, we design systems that are robust against genotypic perturbations (i.e., network perturbations). In other words, we design, using multicanonical Monte Carlo, networks  $W$  whose trajectory on the attractor hardly changes when a small network perturbation  $\delta W$  is added. We define the parameter sensitivity and use it as a guiding function of the robustness.

Sensitivity analysis using parameter sensitivity has been developed and applied in various fields [13, 14]. While most of these studies have dealt with continuous time systems, we define the parameter sensitivity for discrete time systems as follows.

Let us denote the set of elements in  $W$  in Eq. (1) by



**FIG. 3:** (COLOR ONLINE) The two-dimensional density  $D(\lambda_1, \gamma)$  of  $\lambda_1$  and  $\gamma$  for  $N = 10$ ,  $k = 2$  (left) and  $k = 5$  (right). A large fraction of networks with small  $\gamma$  degenerate in the region indicated by the red rectangles. The black lines indicate  $\lambda = 0$ . It should be noted that  $\gamma$  of  $\lambda_1 > 0$  diverges, when  $(T_{max} - T') \rightarrow \infty$ .

a vector  $\mathbf{W}$ . When a small network perturbation  $\delta\mathbf{W}$  is introduced into  $\mathbf{W}$  at  $t = T'$ , the displacement between unperturbed trajectory  $\mathbf{x}^t(\mathbf{W})$  and perturbed trajectory  $\mathbf{x}^t(\mathbf{W} + \delta\mathbf{W})$  is approximated by  $(\partial\mathbf{x}^t/\partial\mathbf{W})\delta\mathbf{W}$ , where  $\partial\mathbf{x}^t/\partial\mathbf{W}$  is a  $N \times N^2$  matrix. We call this matrix the sensitivity matrix  $\Delta^t$ , and the time evolution of  $\Delta^t$  is given by

$$\Delta^{t+1} = \frac{\partial\mathbf{F}}{\partial\mathbf{x}}\Delta^t + \frac{\partial\mathbf{F}}{\partial\mathbf{W}},$$

where  $\partial\mathbf{F}/\partial\mathbf{x}$  is the Jacobian matrix and  $\partial\mathbf{F}/\partial\mathbf{W}$  is the parametric Jacobian matrix. It should be noticed that the two trajectories  $\mathbf{x}^t(\mathbf{W})$  and  $\mathbf{x}^t(\mathbf{W} + \delta\mathbf{W})$  coincide for  $t \leq T'$ , and thus  $\Delta^t = 0$  for  $t \leq T'$ . The growth rate of the displacement between  $\mathbf{x}^t(\mathbf{W} + \delta\mathbf{W})$  and  $\mathbf{x}^t(\mathbf{W})$  with respect to the perturbation vector  $\delta\mathbf{W}$  is obtained by  $\Delta^t\delta\hat{\mathbf{W}}$ , where  $\delta\hat{\mathbf{W}} = \delta\mathbf{W}/|\delta\mathbf{W}|$ . The maximum value of  $|\Delta^t\delta\hat{\mathbf{W}}|$  at time step  $t$  is given by the maximum singular value  $\sigma_1^t$  of  $\Delta^t$  matrix.  $\sigma_1^t$  can be obtained by performing the singular value decomposition of  $\Delta^t$ .  $\sigma_1^t$  diverges for  $t \rightarrow \infty$  when the maximum Lyapunov exponent of the trajectory is positive. On the other hand,  $\sigma_1^t$  oscillates or converges to a constant value when the maximum Lyapunov exponent is negative. Note that no parameters except for  $\mathbf{W}$  are perturbed in this study. Once a network  $\mathbf{W}$  is given,  $\Delta^t$  and its  $\sigma_1^t$  are estimated for each time step. We define parameter sensitivity  $\gamma$  as the logarithm of an average of  $\sigma_1^t$  along the trajectory:

$$\gamma = \ln \left( \frac{\sum_{t=T'}^{T_{max}-1} \sigma_1^t}{T_{max} - T'} \right).$$

Here, we regard the first  $T' - 1$  steps of the trajectory as transient, and discard them. We use  $T' = 1000$  and  $T_{max} = 1500$ .

Our goal is to sample networks with small  $\gamma$ . In order to obtain such networks, we perform random walks in  $\lambda_1$  space with the fixed  $w(\lambda_1)$  estimated above. These random walks facilitate efficient sampling of the networks with small  $\gamma$ . We also obtain the two-dimensional density  $D(\lambda_1, \gamma)$  of  $\lambda_1$  and  $\gamma$  as follows: we construct the two-dimensional histogram  $h(\lambda_1, \gamma)$  through the random walks, and, after  $h(\lambda_1, \gamma)$  is constructed,  $D(\lambda_1, \gamma)$  is calculated by

$$D(\lambda_1, \gamma) \propto \frac{h(\lambda_1, \gamma)}{w(\lambda_1)}.$$

Figure 3 shows  $D(\lambda_1, \gamma)$  for  $N = 10$  with  $k = 2$  and 5. These results show that although networks with small  $\gamma$  can take various values for  $\lambda_1$ , the vast majority of such networks have negative but near zero  $\lambda_1$  (see red rectangles in Fig. 3).

This indicates that, when robustness against network perturbations is optimized, networks with negative but near zero  $\lambda_1$  will appear with high probability. This appearance of systems with marginal stability can be interpreted as self-organization of *the edge of chaos*. In this scenario, the system automatically comes close to *the edge of chaos* without tuning parameters.

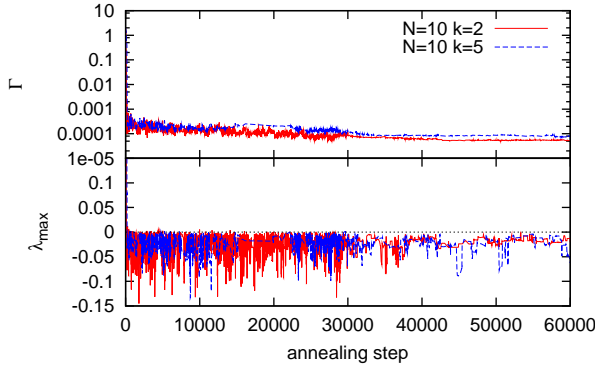
In order to confirm that optimization of mutational robustness leads to the emergence of *the edge of chaos*, we perform simulated annealing. Here, we define a parameter sensitivity  $\Gamma$  without the linear approximation:

$$\Gamma = \left\langle \frac{\sum_{t=T'}^{T_{max}} |\mathbf{x}^t(\mathbf{W} + \delta\mathbf{W}) - \mathbf{x}^t(\mathbf{W})|}{T_{max} - T'} \right\rangle_{\delta\mathbf{W}},$$

where  $\langle \rangle_{\delta\mathbf{W}}$  represents an average over realizations of  $\delta\mathbf{W}$ . We minimize this  $\Gamma$  using the simulated annealing. The average is taken over 100 samples of  $\delta\mathbf{W}$ , and the parameters  $T' = 1000$  and  $T_{max} = 1500$  are used. In each step of the simulated annealing, a transition from the current state  $\mathbf{W}$  to a proposed candidate  $\mathbf{W}'$  is accepted if and only if the ratio  $\exp[-\beta(\Gamma(\mathbf{W}') - \Gamma(\mathbf{W}))]$  is smaller than a random number uniformly distributed in  $(0, 1]$ . Here, the inverse temperature  $\beta$  is a increasing function of simulation step  $n$ . We choose this  $\beta$  as  $\beta = 10n/3$  (for  $n < 30000$ ) and  $\beta = \infty$  (for  $n \geq 30000$ ). Note that the function  $\Gamma$  that we aim to minimize fluctuates due to the finite sample size of  $\delta\mathbf{W}$ , and thus occasionally a worse network could be accepted or a suitable network could be rejected, even for  $\beta = \infty$ .

In Fig.4, we plot  $\lambda_1$  and  $\Gamma$  for networks that are sampled during the simulated annealing. These results indicate that most networks obtained in the last half of the simulations ( $n \geq 30000$ ) are in the region  $-0.05 \leq \lambda_1 < 0$ , and we regard this region as *the edge of chaos*.

In summary, using multicanonical Monte Carlo, we have shown that systems at *the edge of chaos* emerge as a self-organization phenomenon with only the requirement of mutational robustness. We have also performed simulated annealing and confirmed this scenario. We emphasize that no fine tuning of other parameters, such as number of input links  $k$  or model parameters  $(a, \epsilon)$ , is needed.



**FIG. 4:** (COLOR ONLINE) Time series of sensitivity  $\Gamma$  (upper panel) and the maximum Lyapunov exponent  $\lambda_1$  (lower panel) in the course of simulated annealing. The red and blue lines indicate results for  $N = 10$  with  $k = 2$  and  $N = 10$  with  $k = 5$ , respectively.  $\lambda_1$  and  $\Gamma$  are calculated in the same simulations. The inverse temperature is set to be  $\beta = \infty$  in the last half of these simulations.

The emergence of the *edge of chaos* with the requirement of mutational robustness is somehow counterintuitive because mutational robustness seems to be positively correlated with dynamical stability. The mechanism of the emergence of the *edge of chaos*, revealed by multicanonical Monte Carlo, is as follows: when mutational robustness is required, selected systems need to have  $\lambda_1 \leq 0$  because  $\gamma$  for  $\lambda_1 > 0$  diverges as  $t \rightarrow \infty$ . The density  $D(\lambda_1)$  is an increasing function for  $\lambda_1 \leq 0$ . Therefore, the density of networks becomes largest at  $\lambda_1 \sim 0$  under the condition  $\lambda_1 \leq 0$  (see Fig.1): the red rectangles in Fig.3 indicate the degeneracy of a large numbers of net-

works. Due to this degeneracy, systems at the *edge of chaos* are realized in high probability.

Similar results have been found in recent studies [15–17]; systems that have the ability to reach a stable fixed point with transient chaotic behavior appear with only the requirement of robustness against genotypic perturbations. These results can be also interpreted as the emergence of the *edge of chaos*. However, it has not until now been explained why such systems are selected. In this paper, we have proposed a mechanism for the emergence of the *edge of chaos*, namely that the vast majority of stable networks have marginal stability, and thus networks at the *edge of chaos* are selected under random sampling. It is reasonable to think that this degeneracy of marginally stable networks appears whenever parameters are set in the chaotic phase, in which chaotic systems are obtained under random construction of systems for  $N \rightarrow \infty$ . Based on the fact that similar results were found in the previous studies [15–17], most of what we discussed here seems not to depend on the details of a model.

Mutational robustness seems to be a natural requirement for living systems. Therefore our scenario is expected to apply to real living systems. In fact, several recent studies have suggested that gene networks of real organisms stay at the *edge of chaos* [18–22]. Our study provides an explanation: the requirement of mutational robustness drives such organisms to the *edge of chaos*, whether or not staying in such a regime is preferable for living systems.

We would like to acknowledge encouragement and help from Kunihiro Keneko. This work was supported by the Global COE Program (Core Research and Engineering of Advanced Materials-Interdisciplinary Education Center for Materials Science), MEXT, Japan. All simulations were performed on a PC cluster at Cybermedia Center, Osaka University.

- 
- [1] J. Visser, J. Hermisson, G. Wagner, L. Meyers, H. Bagheri-Chaichian, J. Blanchard, L. Chao, J. Cheverud, S. Elena, W. Fontana, et al., *Evolution* **57**, 1959 (2003), ISSN 1558-5646.
  - [2] F. Li, T. Long, Y. Lu, Q. Ouyang, and C. Tang, *Proceedings of the National Academy of Sciences of the United States of America* **101**, 4781 (2004).
  - [3] A. Wagner, *Robustness and evolvability in living systems* (Princeton University Press Princeton, NJ, 2005).
  - [4] J. Masel and M. Trotter, *Trends in Genetics* (2010), ISSN 0168-9525.
  - [5] S. Kauffman, *The origins of order: Self organization and selection in evolution* (Oxford University Press, USA, 1993), ISBN 0195079515.
  - [6] K. Kaneko, *Physica D: Nonlinear Phenomena* **41**, 137 (1990), ISSN 0167-2789.
  - [7] B. A. Berg and T. Neuhaus, *Phys. Lett. B* **267**, 249 (1991).
  - [8] B. A. Berg and T. Celik, *Phys. Rev. Lett.* **69**, 2292 (1992).
  - [9] E. Ott, *Chaos in dynamical systems* (Cambridge Univ Pr, 2002).
  - [10] Throughout this study,  $x_i^{0*} = \sin(i)$  is used. We confirm that the choice of the initial state does not affect the results.
  - [11] B. A. Berg and T. Neuhaus, *Phys. Rev. Lett.* **68**, 9 (1992).
  - [12] F. Wang and D. P. Landau, *Phys. Rev. Lett.* **86**, 2050 (2001).
  - [13] A. Varma, M. Morbidelli, and H. Wu, *Parametric sensitivity in chemical systems* (Cambridge Univ Pr, 1999), ISBN 0521621712.
  - [14] T. Perumal, Y. Wu, and R. Gunawan, *Journal of theoretical biology* **261**, 248 (2009), ISSN 0022-5193.
  - [15] S. Bornholdt and K. Sneppen, *Proceedings of the Royal Society B: Biological Sciences* **267**, 2281 (2000).

- [16] A. Szejka and B. Drossel, The European Physical Journal B-Condensed Matter and Complex Systems **56**, 373 (2007), ISSN 1434-6028.
- [17] V. Sevim and P. Rikvold, Journal of theoretical biology **253**, 323 (2008), ISSN 0022-5193.
- [18] R. Serra, M. Villani, A. Graudenzi, and S. Kauffman, Journal of theoretical biology **246**, 449 (2007).
- [19] I. Shmulevich, S. Kauffman, and M. Aldana, Proceedings of the National Academy of Sciences of the United States of America **102**, 13439 (2005).
- [20] M. Nykter, N. Price, M. Aldana, S. Ramsey, S. Kauffman, L. Hood, O. Yli-Harja, and I. Shmulevich, Proceedings of the National Academy of Sciences **105**, 1897 (2008).
- [21] E. Balleza, E. Alvarez-Buylla, A. Chaos, S. Kauffman, I. Shmulevich, and M. Aldana, PLoS One **3**, e2456 (2008).
- [22] S. Chowdhury, J. Lloyd-Price, O. Smolander, W. Baici, T. Hughes, O. Yli-Harja, G. Chua, and A. Ribeiro, BMC Systems Biology **4**, 143 (2010).